(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 362 942 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
10.07.1996 Bulletin 1996/28

(51) Int Cl.[6]: **C07D 498/04**, C07D 413/04, C07D 417/04
// (C07D498/04, 267:00, 235:00)

(21) Application number: **89202457.1**

(22) Date of filing: **29.09.1989**

(54) Benzoxazepinone process

Benzoxazepinon-Verfahren

Procédé benzoxazépinone

(84) Designated Contracting States:
AT BE CH DE ES FR GB IT LI LU NL SE

(30) Priority: **06.10.1988 GB 8823475**

(43) Date of publication of application:
11.04.1990 Bulletin 1990/15

(73) Proprietor: **MERCK SHARP & DOHME LTD.**
Hoddesdon Hertfordshire EN11 9NU (GB)

(72) Inventors:
- **Houghton, Peter G.**
  Nr. Royston Hertfordshire (GB)
- **Wright, Stanley H. B.**
  Sawbridgeworth Hertfordshire (GB)

(74) Representative: **Cole, William Gwyn et al**
European Patent Department
Merck & Co., Inc.
Terlings Park
Eastwick Road
Harlow Essex CM20 2QR (GB)

(56) References cited:
EP-A- 0 109 921
GB-A- 1 016 526
GB-A- 2 075 012
US-A- 4 622 320
US-A- 4 622 321

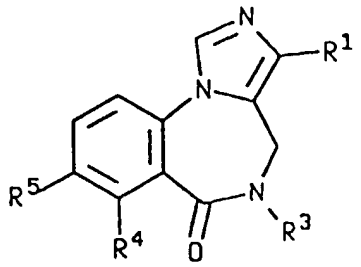
EP 0 362 942 B1

Printed by Jouve, 75001 PARIS (FR)

Description

This invention relates to a class of chemical compounds useful as intermediates and in particular to a class of imidazobenzoxazepinone derivatives. The intermediates are useful in a novel process for the preparation of a class of pharmacologically active imidazobenzodiazepine compounds.

Certain imidazobenzodiazepines having anxiolytic, anticonvulsant, muscle-relaxant and sedativehypnotic properties are disclosed in European patent specification No. 150,040. That specification discloses, inter alia, compounds having the formula I:



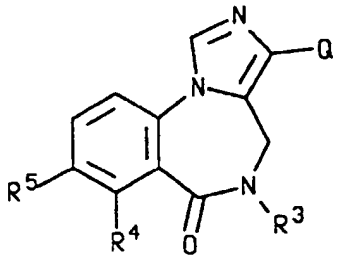
(I)

in which R^1 is a 5- or 6-membered aromatic heterocyclic group; R^3 represents hydrogen or lower alkyl; and R^4 and R^5 each independently signify hydrogen, halogen, trifluoromethyl, cyano, nitro, amino or lower alkyl.

European patent specification No. 109,921 describes a group of compounds within the formula I above in which R^1 represents an oxadiazolyl group, having a C_{1-3} alkyl substituent. Furthermore, U.S. Patents Nos. 4,622,320 and 4,622,321 disclose further compounds within general formula I in which R^1 represents a cyclopropylsubstituted oxadiazolyl group.

British patent specification Nos. 1,016,526 and 2,075,012 describe benzoxazepindione and imidazobenzoxazepine derivatives, respectively, and processes for their preparation by cyclization.

The processes described in the above patents for the preparation of compounds of type I above start from an imidazobenzodiazepine nucleus of formula II:

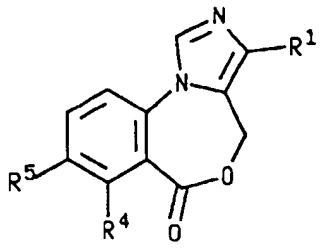


(II)

in which Q represents a group which may be converted into a heterocyclic group R^1. Thus the heterocyclic ring is incorporated in the final synthetic step.

The present invention is based on a novel imidazobenzoxazepine ring system which includes a heterocyclic substituent and which may then be converted into a heterocyclyl-substituted imidazobenzodiazepine.

Accordingly the present invention provides a compound of formula III:



(III)

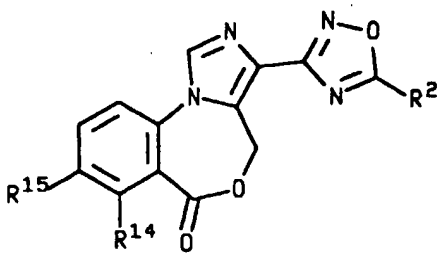
wherein R^4 and R^5 each independently signify hydrogen, halogen trifluoromethyl, cyano, nitro, amino or C_{1-6} alkyl

Preferred groups R^4 and R^5 are hydrogen, halogen or trifluoromethyl, in particular hydrogen, fluoro, chloro or bromo.

The group R^1 represents an aromatic heterocyclic ring containing 5 or 6 atoms, up to three of which may be selected from oxygen, nitrogen and sulphur. Suitable groups R^1 include oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, pyrazinyl and pyrimidinyl. Particularly suitable groups R^1 are 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazole-2-yl, 1,2,4-thiadiazol-3-yl, 1,3,4-thiadiazol-2-yl and 1,2,5-thiadiazol-3-yl.

The aromatic heterocyclic group R^1 may be unsubstituted or substituted on a carbon atom. Suitable substituents include C_{1-5} alkyl, C_{3-6} cycloalkyl, trifluoromethyl, phenyl, amino, C_{1-6} alkylamino, C_{1-6} alkoxy(C_{1-6})alkyl or hydroxy. Preferred substituents for the group R^1 are C_{1-4} alkyl, such as methyl, ethyl, n-propyl, isopropyl and t-butyl; and C_{3-6} cycloalkyl, especially cyclopropyl.

One sub-group of compounds of this invention is represented by formula IV:

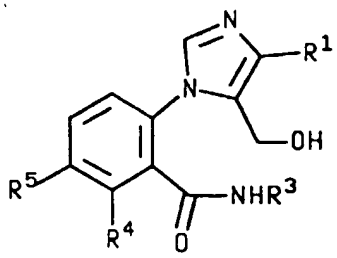


(IV)

wherein R^{14} and R^{15} independently represent hydrogen, fluoro, chloro or bromo; and R^2 represents hydrogen, C_{1-4} alkyl or C_{3-6} cycloalkyl. Preferably R^2 represents hydrogen, methyl, n-propyl, isopropyl, t-butyl or cyclopropyl.

The benzoxazepinone compounds of this invention are valuable intermediates for the preparation of benzodiazepines of formula I above. Accordingly the present invention also provides a process for the preparation of a compound of formula I above, which process comprises the following steps:

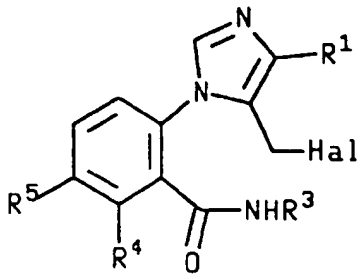
a) aminolysis of a benzoxazepinone of formula III to form an amide of formula V:



(V)

wherein R^1, R^4 and R^5 are as defined above with reference to formula I; and R^3 represents hydrogen or C_{1-6} alkyl;

b) halogenation of compound V to form a compound of formula VI:



(VI)

wherein R^1, R^3, R^4 and R^5 are as defined above; and Hal represents chlorine or bromine; and

c) cyclisation of compound VI to form a compound of formula I.

The compounds V and VI are also novel and represent further aspects of this invention.

Furthermore the steps a), b) and c) above each represent novel processes individually and each forms a further aspect of this invention.

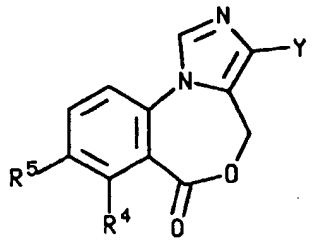
Process a) of the synthetic sequence comprises the aminolysis of a benzoxazepinone of formula III. Suitable reagents for this process are ammonia or C_{1-6} alkylamine, such as methylamine, propylamine or butylamine. The amine is chosen to provide the nitrogen substituent group R^3 in the final product of formula I. The process may be carried out in a polar solvent such as ethanol, water, dimethylformamide, or mixtures thereof. Ambient temperatures are suitable for this process, for example from 15°C to 30°C, especially 20°C to 25°C.

Process b) of the synthetic sequence comprises the halogenation of the compound V to give a haloamide of formula VI. Any suitable halogenating agent may be employed in this process. Preferably, the halogen group Hal in formula VI is chlorine. Suitable chlorinating agents include thionyl chloride, methanesulphonyl chloride and phosphorus oxychloride. The reaction may be carried out in an inert anhydrous solvent such as tetrahydrofuran or dimethylformamide, suitably at a temperature of from 0°C to 25°C.

Process c) of the synthetic sequence comprises the cyclisation of compound VI to form a benzodiazepine of formula I. Suitably this cyclisation is effected by means of a strong organic base, such as sodium hydride or potassium t-butoxide. The temperature at which the process is carried out is dependent on the base used. For example, potassium t-butoxide is employed at low temperatures, such as -40°C to -20°C. A suitable solvent is tetrahydrofuran. Sodium hydride may be used at ambient or elevated temperatures such as 20°C to 100°C. A suitable solvent is again tetrahydrofuran.

The final product of formula I may be isolated by conventional methods such as crystallisation, solvent extraction or chromatography.

The benzoxazepinone compounds of formula III of this invention may be prepared from a compound of formula VII:



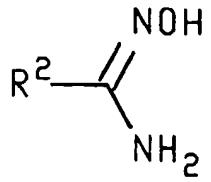
(VII)

wherein R^4 and R^5 are as defined above: and Y represents a group which may be converted into a 5- or 6-membered aromatic heterocyclic ring.

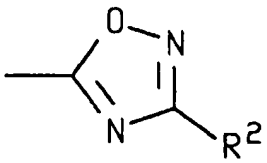
The process for converting the group Y into a 5- or 6-membered aromatic heterocyclic ring may be carried out by conventional methods. Examples of suitable groups Y include -CN, $-CONH_2$, $-C(NH_2)=NOH$ and $-COR^a$; where R^a represents a leaving group, e.g. C_{1-6} alkoxy.

In particular, compounds of formula III in which the group R^1 represents oxadiazolyl may be prepared by:

(i) reacting a reactive derivative of a compound of formula VII above wherein Y represents $-CO_2H$, with a compound of formula:

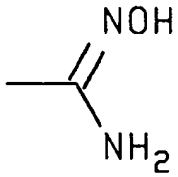


wherein R^2 is as defined with respect to formula IV above, to form a compound of formula III wherein R^1 is:

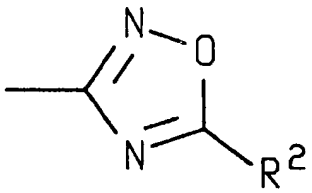


in which R^2 is as defined above; or

(ii) reacting a compound of formula VII above where Y represents -CN, with hydroxylamine or a salt thereof, e.g. the hydrochloride, to form a compound of formula VII where Y represents:



and reacting that product with an anhydride of formula $(R^2CO)_2O$, where R^2 is as defined with respect to formula IV above, to form a compound of formula III wherein R^1 is:



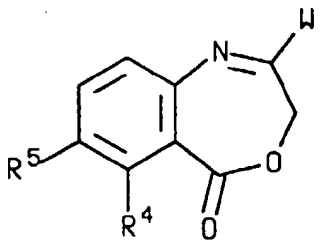
in which R^2 is as defined above.

Process (i) above may be carried out at a temperature of from 20°C to 150°C for a time of from 1 to 5 hours. Suitable solvents include tetrahydrofuran, dimethylformamide, toluene and xylene.

In process (ii), the reaction with hydroxylamine may be carried out in a polar solvent such as ethanol or isopropanol, suitably at reflux temperature, for a time of from 3 hours to 4 days. The subsequent reaction with the anhydride may be carried out with the anhydride reactant itself acting as solvent, suitably at a temperature of from 80°C to 160°C, for a time of from 1 to 6 hours.

Other examples of the group Y which may be converted into a 5- or 6-membered aromatic heterocyclic ring are the same as the group Q in European patent specification No. 150,040.

The benzoxazepinone compounds of formula III may also be prepared by reacting a compound of formula VIII:



(VIII)

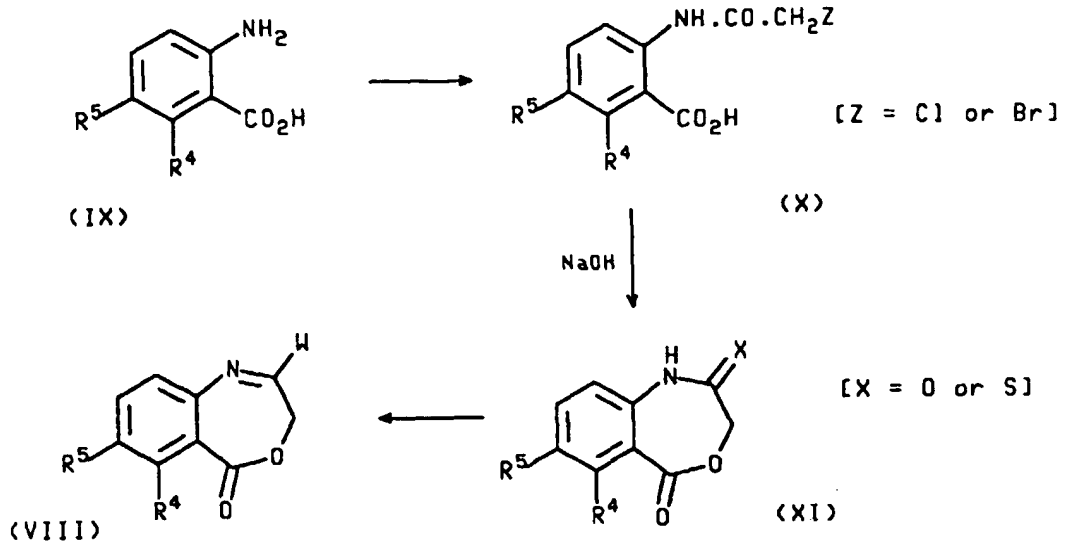
where R^4 and R^5 are as defined above, and W represents a leaving group; with an isocyanide of formula $CN\text{-}CH_2\text{-}R^1$

in the presence of a base.

Suitable bases for this reaction include lithium diisopropylamide and potassium hexamethyldisilazide. The leaving group W is preferably chlorine.

The compound of formula VII may also be prepared from the compound VIII above by reaction thereof with an isocyanide of formula $CN\text{-}CH_2\text{-}Y$ in the presence of a base, e.g. triethylamine.

The benzoxazepinone of formula VIII may be prepared by the following reaction sequence:



Treatment of the anthranilic acid IX with either chloroacetyl chloride or bromoacetyl bromide in dimethylformamide at room temperature provides the amide X. The amide X is then cyclised to give the benzoxazepine XI. This cyclisation may be carried out by heating the amide alone in refluxing dimethylformamide or by the use of a base, for example potassium fluoride in acetonitrile, potassium carbonate in methyl ethyl ketone, or, preferably, sodium hydroxide in isopropyl alcohol.

Treatment of the dione XI, X=O, with phosphoryl chloride and N,N-dimethylaniline in dichloromethane yields the imidoyl chloride VIII, W=Cl.

Alternatively, treatment of the thione XI, X=S, with sodium hydride followed by methyl iodide in tetrahydrofuran provides an imidothiolic ester VIII, W=SMe.

The following Examples illustrate the processes and compounds of this invention:

PREPARATION A

3-Isocyanomethyl-5-isopropyl-1,2,4-oxadiazole

a) Formamidoacetonitrile

Aminoacetonitrile hydrochloride (348 g) in boiling methyl formate (1.88 l) was treated with triethylamine (570 ml), added over 10 minutes, and the mixture heated under reflux for 22 hours. The mixture was cooled to 0°C and the triethylamine hydrochloride removed by filtration and washed with ethyl acetate. The filtrate was washed with saturated potassium carbonate (300 ml), dried and evaporated. The residue was distilled (short-path) at 135°C/0.1 mm to give the product (211 g, 67%).

b) Formamidoacetamidoxime

Sodium metal (20.7 g) was dissolved in dry methanol (259 ml) and the resulting solution added to a hot solution of hydroxylamine hydrochloride (62.1 g) in dry methanol (448 ml). The resulting mixture was stirred and heated under reflux for 10 minutes and then cooled to room temperature. The mixture was filtered to remove sodium chloride and the filtrate was then added to formamidoacetonitrile (37.8 g) at 5°C. The solution was then placed in the cold room for several days to yield the product as a highly crystalline white solid, 40 g, 76% yield obtained in two crops.

c) 3-Formamidomethyl-5-isopropyl-1,2,4-oxadiazole

Sodium metal (2.3 g) was dissolved in absolute ethanol (500 ml) and then formamidoacetamidoxime (50 g) and dried 4A molecular sieves (50 g) added. The mixture was stirred at room temperature for 5 minutes and then ethyl isobutyrate (118 ml) added. The resulting mixture was heated under reflux under nitrogen atmosphere for 6 hours and then cooled to room temperature. The mixture was filtered through Hyflo to remove the sieves and then the solvent removed in vacuo at 40°C. The residue was dissolved in dichloromethane (500 ml) and treated with charcoal (5 g) and Na_2SO_4 (5 g). The mixture was filtered through Hyflo and the solvent removed in vacuo to yield the product as a dark oil, 46.3 g, 64%. Purity 85-90% (NMR).

d) 3-Isocyanomethyl-5-isopropyl-1,2,4-oxadiazole

Formamidomethyloxadiazole (24.1 g) was dissolved in dichloromethane (156 ml) containing triethylamine (90 ml) at -20°C. Phosphoryl chloride (13.3 ml) was added dropwise over 10 minutes keeping the temperature below -5°C for 1 hour. A solution of sodium carbonate (21.4 g) in water (120 ml) was added at <5°C and the mixture stirred at room temperature for 1 hour. The mixture was filtered and the filtrate liquors separated. The aqueous layer was extracted with dichloromethane (2 x 50 ml). The organic layers were combined and washed with brine (100 ml), dried (Na_2SO_4) and evaporated to give a dark coloured oil. The oil was distilled (90°C, 0.4 mmHg) to give the product as a pale yellow oil, 13.2 g, 64% yield. Purity >99% (by NMR and LC).

EXAMPLE 1

4,1-Benzoxazepin-2,5-dione (XI; R^4=R^5=H, X=O)

A solution of sodium hydroxide (2 g, 50 mole) in water (12 ml) was added to a stirred slurry of 2-chloroacetamido-benzoic acid (10.3 g, 48 mmole) in isopropanol (22.5 ml) and water (87.5 ml). The mixture was stirred until a solution formed and then heated at 80°C for 4 hours. The solution was cooled to 0°C and the crystalline solid collected, washed with water and dried in vacuo at 50°C to give the product (7.4 g, 87%), m.p. 200-201°C.

EXAMPLE 2

6-Chloro-4,1-benzoxazepin-2,5-dione (XI; R^4=Cl, R^5=H, X=O)

Chloroacetyl chloride (51 ml, 0.64 mole) was added dropwise to a solution of 2-amino-6-chlorobenzoic acid (100 g, 0.58 mole) in dimethylformamide (150 ml) at <30°C. The solution was stirred for 1 hour at <30°C and then treated with a solution of sodium hydroxide (52.2 g, 1.3 mole) in water (1.25 l). The mixture was stirred for 15 minutes, then heated to 90°C to dissolve the solid and solution maintained at 90°C for 2 hours. The solution was cooled to 0°C and the crystalline solid collected, washed with water and dried in vacuo at 50°C to give the product (111.7 g, 91%), m.p. 193-196°C.

EXAMPLE 3

4,1-Benzoxazepin-5-one-2-thione (XI; R^4=R^5=H, X=S)

4,1-Benzoxazepin-2,5-dione (4.5 g, 25 mmole) in dimethoxyethane (125 ml) was treated with Lawesson's reagent (12 g, 30 mmole) and the mixture was stirred at room temperature for 24 hours. The solution was filtered and the filtrate evaporated. The residue in ethyl acetate was washed with sodium bicarbonate solution and dried (Na_2SO_4). The ethyl acetate solution was diluted with hexane and filtered through silica. The filtrate was evaporated to give the thione (4.5 g, 92%), m.p. 174-178°C.

EXAMPLE 4

6-Chloro-4,1-benzoxazepin-5-one-2-thione (XI; R^4=Cl, R^5=H, X=S)

6-Chloro-4,1-benzoxazepin-2,5-dione (10.6 g, 50 mmole) in dimethoxyethane (250 ml) was treated with Lawesson's reagent (12.1 g, 30 mmole) and the mixture stirred at room temperature for 24 hours. The solution was filtered and evaporated. The residue in ethyl acetate was washed with sodium bicarbonate solution and dried (Na_2SO_4). The solution was diluted with hexane and filtered through silica. The filtrate was evaporated to give the product (11.1 g,

97%), m.p. 177-180°C.

EXAMPLE 5

5,6-Dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine-3-carbonitrile (VII; R^4=R^5=H, Y=CN)

4,1-Benzoxazepin-2,5-dione (2.1 g, 12 mmole), N,N-dimethylaniline (13.7 ml) and phosphoryl chloride (1.75 ml, 18 mmole) in dichloromethane (20 ml) was heated under reflux for 18 hours. The solution was cooled and poured into water (50 ml) containing sodium bicarbonate (8 g). The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic phases were washed with water, dried (Na_2SO_4) and concentrated to give a solution of the imidoyl chloride (VIII; R^4=R^5=H, W=Cl) in dimethylaniline.

Formamidoacetonitrile (2.2 g, 26 mmole) and triethylamine (8.7 ml) in dichloromethane (26 ml) was treated with phosphoryl chloride (2.5 ml, 25 mmole) at -25°C and the mixture stirred for 1 hour. The mixture was treated with sodium carbonate (5.3 g) in water (25 ml) at -5°C and stirred for 45 minutes. The organic layer was separated, washed with water and dried (Na_2SO_4) to give a solution of isocyanoacetonitrile in dichloromethane.

The isonitrile solution was added to the imidoyl chloride solution containing triethylamine (4.5 ml) and stirred at room temperature for 18 hours. The mixture was poured into 2N HCl (50 ml), the organic layer separated, washed with 2N HCl, saturated sodium bicarbonate and dried (Na_2SO_4). The solution was evaporated and the residue stirred with hot t-butyl methyl ether. The mixture was cooled and the solid collected, washed with t-butyl methyl ether and dried *in vacuo* to give the product (1.6 g, 46%), m.p. 220-221°C.

EXAMPLE 6

7-Chloro-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine-3-carbonitrile (VII; R^4=Cl, R^5=H, Y=CN)

6-Chloro-4,1-benzoxazepin-2,5-dione (25 g, 0.118 mole), phosphoryl chloride (17.5 ml, 0.188 mole) and N,N-dimethylaniline (137 ml, 1.09 mole) in dichloromethane (240 ml) were heated under reflux for 18 hours. The solution was cooled and poured into water (470 ml) containing sodium bicarbonate (82.5 g). The organic layer was washed with water, dried (Na_2SO_4) and concentrated to give a solution of the imidoyl chloride (VIII; R^4=Cl, R^5=H, W=Cl) in dimethylaniline.

Formamidoacetonitrile (22.3 g, 0.265 mole) in dichloromethane (263 ml) containing triethylamine (87.2 ml, 0.626 mole) was cooled to -25°C and phosphoryl chloride (24.8 ml, 0.266 mole) added slowly over ½ hour. The mixture was stirred at -20°C for a further 1 hour and then Na_2CO_3 (52.6 g) in water (263 ml) was added at below -5°C. The mixture was filtered, the organic layer separated, washed with water and dried to give a solution of isocyanoacetonitrile in dichloromethane.

The solution of the imidoyl chloride in N,N-dimethylaniline was stirred at room temperature with triethylamine (40 ml, 0.288 mole) and the solution of the isocyanoacetonitrile added over 5 minutes. The reaction exothermed from 17.5°C to 24.5°C over a period of 2 hours and was stirred overnight at room temperature. The dark reaction mixture was poured into 2N hydrochloric acid (500 ml) and stirred for 5 minutes before separating the organic layer. This was washed with 2N hydrochloric acid (300 ml), saturated sodium bicarbonate solution, dried (Na_2SO_4) and evaporated. The solid was swished with boiling t-butyl methyl ether (75 ml) for 1 hour, and cooled in ice for a further 1 hour. The solid was collected, washed with the minimum of t-butyl methyl ether and dried in air to give the product as a light green crystalline solid (18.3 g, 60%), m.p. 217-219°C.

EXAMPLE 7

5,6-Dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine-3-amidoxime

5,6-Dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine-3-carbonitrile (3.8 g, 0.017 mole), potassium carbonate (2.9 g, 0.02 mole), hydroxylamine hydrochloride (1.46 g, 0.02 mole) and water (2.9 ml) were stirred in isopropanol (190 ml) at room temperature for 4 days. The mixture was heated under reflux for 6 hours and then concentrated to 50 ml. The solution was cooled to 5°C and water (47 ml) added slowly to complete the crystallisation. The solid was collected, washed with water and dried *in vacuo* at 40°C to give the product (3.75 g, 86%), m.p. 222-224°C.

EXAMPLE 8

7-Chloro-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine-3-amidoxime

A mixture of 7-chloro-5,6-dihydro-6-oxo-4H-imidazo[l,5-a][4,1]benzoxazepine-3-carbonitrile (16.86 g, 0.06 mole), potassium carbonate (13.5 g, 0.9 mole) and hydroxylamine hydrochloride (4.6 g, 0.06 mole) in isopropanol (843 ml) containing water (13.5 ml) was stirred at room temperature for 4 days. The reaction mixture was then concentrated to a volume of 256 ml by distillation, cooled to room temperature and water (256 ml) added. The resulting mixture was cooled at 0°C for 1 hour and the solid collected, washed with water and dried in vacuo at 50°C to give the product (12 g, 63%), m.p. 252-254°C.

EXAMPLE 9

3-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine (III)

5,6-Dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine-3-amidoxime (2 g, 8 mmole) in isobutyric anhydride (6 ml) was heated at 150°C for 1.5 hours. The crude product in ethyl acetate:hexane (1:1) was chromatographed on silica and then crystallised from ethyl acetate:hexane to give the product (1.4 g, 58%), m.p. 143-144°C.

EXAMPLE 10

3-(5-tert-Butyl-1,2,4-oxadiazol-3-yl)-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine (III)

5-6-Dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine-3-amidoxime (1.9 g, 7 mmole) in trimethylacetic anhydride (6 ml) was heated at 150°C for 1 hour. The crude product in ethyl acetate:hexane (1:1) was chromatographed and then crystallised from ethyl acetate to give the product (1.6 g, 66%), m.p. 210-211°C.

EXAMPLE 11

7-Chloro-3-(5-methyl-1,2,4-oxadiazol-3-yl)-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine (III)

7-Chloro-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine-3-amidoxime (3 g, 0.01 mole) in acetic anhydride (9 ml) was heated at 150°C for 3 hours. The crude product in ethyl acetate was chromatographed on silica and then crystallised from acetone to give the product (2.1 g, 66%), m.p. 253-255°C.

EXAMPLE 12

7-Chloro-3-(5-propyl-1,2,4-oxadiazol-3-yl)-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine (III)

7-Chloro-5,6-dihydro-6-oxo-4H-imidazo[1,5 a][4,1]benzoxazepine-3-amidoxime (2 g, 7 mmole) in n-butyric anhydride (6 ml) was heated at 150°C for 1 hour. The crude product was chromatographed on silica, initially with ethyl acetate:hexane (1:1) and then changing to ethyl acetate. The purified product was crystallised from ethyl acetate: cyclohexane (4:1) to give the product (1.2 g, 50%), m.p. 130-132°C.

EXAMPLE 13

7-Chloro-3-(5-pentyl-1,2,4-oxadiazol-3-yl)-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine (III)

7-Chloro-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine-3-amidoxime (2 g, 7 mmole) in caproic anhydride (8 ml) was heated at 150°C for 30 minutes. The crude product in ethyl acetate:hexane (1:1) was chromatographed on silica to give the product (1.6 g, 63%), m.p. 110-112°C.

EXAMPLE 14

7-Chloro-3-(5-isopropyl-1,2,4-oxadiazole-3-yl)-5-6-dihydro-6-oxo-4H-imidazo[1,5-a][[4,1]benzoxazepine (III)

Method A

7-Chloro-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine-3-amidoxime (12.6 g, 0.04 mole) in isobutyric anhydride (38 ml) was heated at 150°C for 1 hour. The crude product in ethyl acetate:hexane (1:1) was chromatographed on silica and crystallised from ethyl acetate to give the product (8.7 g, 60%), m.p. 167-168°C.

Method B

6-Chloro-4,1-benzoxazepin-2,5-dione (1.9 g, 10 mmole), N,N-dimethylaniline (12.4 ml) and phosphoryl chloride (1.6 ml, 16 mmole) in dichloromethane (20 ml) were heated under reflux for 18 hours. The solution was cooled, poured into water (50 ml) containing sodium bicarbonate (7 g) and the organic phase separated. The aqueous phase was extracted with dichloromethane and the combined phases washed with water, dried (Na_2SO_4) and concentrated to give a solution of the imidoyl chloride. The solution was added to a solution of 3-isocyanomethyl-5-isopropyl-1,2,4-oxadiazole (1.5 g, 10 mmole) in tetrahydrofuran (33 ml). The solution was cooled to -78°C and treated with lithium diisopropylamide in cyclohexane (1.5 M, 7.4 ml). The solution was stirred at -70°C for 15 minutes and then at room temperature for 4 hours. The mixture was poured into 2N HCl (50 ml) and the organic layer separated. The aqueous layer was extracted with ethyl acetate and the combined organic layers washed with sodium bicarbonate solution, dried (Na_2SO_4) and evaporated. The crude product in ethyl acetate:hexane (2:1) was chromatographed on silica and crystallised from ethyl acetate to give the product (1.3 g, 43%), m.p. 167-168°C.

Method C

6-Chloro-4,1-benzoxazepin-5-one-2-thione (6.8 g, 30 mmole) in THF (60 ml) was treated with sodium hydride (0.8 g, 33 mmole) suspended in THF (50 ml) at 10°C. The mixture was aged at 10°C for 1 hour, treated with methyl iodide (2 ml, 31 mmole) and stirred for a further hour.

The solution of the S-methyl compound was cooled to -78°C, 3-isocyanomethyl-5-isopropyl-1,2,4-oxadiazole (5.6 g, 37 mmole) added followed by lithium diisopropylamide [from butyl-lithium in hexane (2.4 M, 22 ml) and diisopropylamine (7.6 ml) in THF (41 ml)]. The mixture was stirred at <-65°C for 1.5 hours and then quenched with acetic acid (5 ml). The solution was poured into ethyl acetate (100 ml) and water (100 ml), the organic layer separated and washed with water. The solution was evaporated and the crude product in ethyl acetate:hexane (2:1) chromatographed on silica and crystallised from ethyl acetate to give the product (5.5 g, 53%), m.p. 167-168°C.

EXAMPLE 15

1-(3-Chloro-2-propylcarboxamidophenyl)-5-hydroxymethyl-4-(5-isopropyl-1,2,4-oxadiazol-3-yl)-imidazole (V)

7-Chloro-3-(5-isopropyl-1,2,4-oxadiazol-3-yl)-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine (4 g, 12 mmole) in DMF (20 ml) was treated with excess propylamine and stirred at room temperature for 3 days. The mixture was poured into water and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and evaporated. The residue was triturated with diethyl ether to give the product (3.5 g, 75%), m.p. 158-159°C.

EXAMPLE 16

1-(3-Chloro-2-butylcarboxamidophenyl)-5-hydroxymethyl-4-(5-isopropyl-1,2,4-oxadiazol-3-yl)imidazole (V)

7-Chloro-3-(5-isopropyl-1,2,4-oxadiazol-3-yl)-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine (3.5 g, 10 mmole) in DMF (20 ml) was treated with excess butylamine and stirred at room temperature for 3 days. The mixture was poured into water and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and evaporated. The residue was crystallised from ethyl acetate to give the product (2.5 g, 60%), m.p. 127-128°C.

EXAMPLE 17

1-(3-Chloro-2-methylcarboxamidophenyl)-5-chloromethyl-4-(5-isopropyl-1,2,4-oxadiazol-3-yl)imidazole (VI)

7-Chloro-3-(5-isopropyl-1,2,4-oxadiazol-3-yl)-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine (5 g, 14.5 mmole) in dimethylformamide (25 ml) was treated with excess methylamine at room temperature for 3 hours. The solution of the hydroxymethyl compound was heated in vacuo at 40°C to remove methylamine and then cooled to 0°C. Thionyl chloride (1.3 ml, 18 mmole) was added and the solution stirred at 0°C for 20 minutes. Water (50 ml) was added to the cold solution and the slurry stirred for 2 hours to complete crystallisation. The solid was collected, washed with water and dried in vacuo at 60°C to give the product (5.3 g, 93%), m.p. 176-178°C.

EXAMPLE 18

1-(3-Chloro-2-propylcarboxamidophenyl)-5-chloromethyl-4-(5-isopropyl-1,2,4-oxadiazol-3-yl)-imidazole (VI)

1-(3-Chloro-2-propylcarboxamidophenyl)-5-hydroxymethyl-4-(5-isopropyl-1,2,4-oxadiazol-3-yl)imidazole (3 g, 7 mmole) in THF (20 ml) was treated with thionyl chloride (0.6 ml, 8 mmole) and the mixture stirred for 1 hour. The solid was collected, washed with THF and dried in vacuo at 50°C to give the product (3.1 g, 99%), m.p. 164-167°C.

EXAMPLE 19

1-(3-Chloro-2-butylcarboxamidophenyl)-5-chloromethyl-4-(5-isopropyl-1,2,4-oxadiazol-3-yl)imidazole (VI)

1-(3-Chloro-2-butylcarboxamidophenyl-5-hydroxymethyl-4-(5-isopropyl-1,2,4-oxadiazol-3-yl)imidazole (2.4 g, 6 mmole) in THF (20 ml) was treated with thionyl chloride (0.5 ml, 7 mmole) and the mixture stirred for 1 hour. Water (50 ml) was added, the solid collected, washed with water and recrystallised from ethyl acetate to give the product (2.4 g, 95%), m.p. 149-150°C.

EXAMPLE 20

7-Chloro-3-(5-isopropyl-1,2,4-oxadiazol-3-yl)-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine (I)

1-(3-Chloro-2-methylcarboxamidophenyl)-5-chloromethyl-4-(5-isopropyl-1,2,4-oxadiazol-3-yl)imidazole (2 g, 5 mmole) in THF (50 ml) at -30°C was treated with potassium t-butoxide (0.75 g, 6.25 mmole) in THF (100 ml) and stirred at -30°C for 15 minutes. Acetic acid (1 ml) was added, the solution diluted with water and the solid collected. The solid was chromatographed on silica with ethyl acetate:hexane (1:1) and then ethyl acetate to give the crude product which was crystallised from ethyl acetate to give the product (1.3 g, 72%), m.p. 165°C. $M^{+\cdot}$ = 357.

EXAMPLE 21

7-Chloro-3-(5-isopropyl-1,2,4-oxadiazol-3-yl)-5,6-dihydro-5-propyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine (I)

1-(3 Chloro-2-propylcarboxamidophenyl)-5-chloromethyl-4-(5-isopropyl-1,2,4-oxadiazol-3-yl)-imidazole (2.1 g, 5 mmole) in THF (100 ml) at -30°C was treated with potassium t-butoxide (0.6 g, 5 mmole) in THF (55 ml) added over 30 minutes. The solution was poured into water and extracted with ethyl acetate. The extract was concentrated and the solution crystallised. The solid was collected and dried in vacuo at 50°C to give the product (1.2 g, 60%), m.p. 161-163°C. $M^{+\cdot}$ = 385.

EXAMPLE 22

7-Chloro-3-(5-isopropyl-1,2,4-oxadiazol-3-yl)-5,6-dihydro-5-butyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine (I)

1-(3-Chloro-2-butylcarboxamidophenyl)-5-chloromethyl-4-(5-isopropyl-1,2,4-oxadiazol-3-yl)imidazole (1.75 g, 4 mmole) in THF (87 ml) at -30°C was treated with potassium t-butoxide (0.5 g, 5 mmole) in THF (50 ml) added over 1 hour. Acetic acid (2 ml) was added, the solution poured into water and extracted with ethyl acetate. The extract was washed with water, dried (Na_2SO_4), evaporated and the residue triturated with pentane. The solid was chromatographed on silica with ethyl acetate:hexane (3:2) and the crude product crystallised from ethyl acetate-hexane to give the product (1.0 g, 64%), m.p. 118-119°C. M+1 = 400.

EXAMPLE 23

6-Bromo-4,1-benzoxazepin-2,5-dione (XI; R^4=Br, R^5=H, X=O)

A solution of sodium hydroxide (3.25 g, 81 mmole) in water (20 ml) was added to a stirred slurry of 2-bromo-6-(chloroacetamido)benzoic acid (23 g, 79 mmole) in isopropanol (36 ml) and water (142 ml). The mixture was stirred until a solution formed and then heated at 80°C for 4 hours. The solution was cooled to 0°C and the crystalline solid collected, washed with water and dried in vacuo at 50°C to give the product (18.1 g, 90%), m.p. 210-212°C.

EXAMPLE 24

7-Bromo-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine-3-carbonitrile (VII; R^4=Br, R^5=H, Y=CN)

6-Bromo-4,1-benzoxazepin-2,5-dione (7.23 g, 28 mmole), N,N-dimethylaniline (32.7 ml) and phosphoryl chloride (4.2 ml, 43 mmole) in dichloromethane (48 ml) was heated under reflux for 18 hours. The solution was cooled and poured into water (120 ml) containing sodium bicarbonate (19 g). The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic phases were washed with water, dried (Na_2SO_4) and concentrated to give a solution of the imidoyl chloride (VIII; R^4=Br, R^5=H, W=Cl) in dimethylaniline.

Formamidoacetonitrile (5.23 g, 62 mmole) and triethylamine (21 ml) in dichloromethane (62 ml) was treated with phosphoryl chloride (6 ml, 65 mmole) at -25°C and the mixture stirred for 1 hour. The mixture was treated with sodium carbonate (12.62 g) in water (60 ml) at -5°C and stirred for 45 minutes. The organic layer was separated, washed with water and dried (Na_2SO_4) to give a solution of isocyanoacetonitrile in dichloromethane.

The isonitrile solution was added to the imidoyl chloride solution containing triethylamine (10.5 ml) and stirred at room temperature for 18 hours. The mixture was poured into 2N HCl (120 ml), the organic layer separated, washed with 2N HCl, saturated sodium bicarbonate and dried (Na_2SO_4). The solution was evaporated and the residue stirred with hot t-butyl methyl ether and dried in vacuo to give the product (4.69 g, 55%), m.p. 204-6°C.

EXAMPLE 25

7-Bromo-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine-3-amidoxime

7-Bromo-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine-3-carbonitrile (4 g, 13 mmole), potassium carbonate (2.26 g, 16.4 mmole), hydroxylamine hydrochloride (1.14 g, 16.4 mmole) and water (2.26 ml) were stirred in isopropanol (148 ml) at room temperature for 3 days. The mixture was concentrated to 50 ml. The solution was cooled to 5°C and water (50 ml) added slowly to complete the crystallisation. The solution was collected, washed with water and dried in vacuo at 40°C to give the product (3.35 g, 76%), m.p. >240°C.

EXAMPLE 26

7-Bromo-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine

A solution of 7-bromo-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine-3-amidoxime (2.43 g, 7.2 mmole) and triethylamine (1.5 ml) in dry tetrahydrofuran (75 ml) was cooled with stirring to 5°C. Cyclopropyl carbonyl chloride (0.83 ml, 1.25 equivs.) was added dropwise under N_2 atmosphere and the resulting mixture aged at 5°C for 5 minutes and then allowed to warm to room temperature. After 30 minutes at room temperature, TLC (CH_2Cl_2/MeOH, 95/5) showed the reaction to be complete. The solvent was removed in vacuo to give a solid (2.56 g). Part of this solid (2.47 g) was suspended in xylene (250 ml) containing p-toluenesulphonic acid (0.25 g) and then the mixture was heated to reflux using a Dean and Stark apparatus for 18 hours. The solvent was evaporated and the residue partitioned between water (25 ml) and dichloromethane (25 ml). The aqueous layer was re-extracted with dichloromethane (6 x 30 ml). The organic extracts were combined, dried (Na_2SO_4) and evaporated to give a yellow foam. Trituration with diethyl ether gave the product (1.69 g, 63% overall) as a solid, m.p. 204-8°C.

EXAMPLE 27

3-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine

A solution of 5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine-3-amidoxime (1.66 g, 6 mmole) and triethyl-

amine (1.36 ml) in dry tetrahydrofuran (50 ml) was cooled with stirring to 5°C. Cyclopropyl carbonyl chloride (0.73 ml, 1.25 equivs.) was added dropwise under N_2 atmosphere and the resulting mixture aged at 5°C for 5 minutes and then allowed to warm to room temperature, when TLC (CH_2Cl_2/MeOH, 95/5) showed the reaction to be complete. The solvent was removed in vacuo to give a yellow solid (1.75 g). The solid was suspended in xylene (250 ml) containing p-toluenesulphonic acid (0.18 g) and then the mixture was heated to reflux using a Dean and Stark apparatus for 20 hours. The solvent was evaporated and the residue partitioned between water (25 ml) and dichloromethane (25 ml). The aqueous was re-extracted with dichloromethane (6 x 30 ml). The organic extracts were combined, dried (Na_2SO_4) and evaporated to give a yellow foam. Trituration with diethyl ether gave the product (1.26 g, 76%) as a beige solid, m.p. 206-209°C.

EXAMPLE 28

1-(3-Bromo-2-methylcarboxamidophenyl)-5-chloromethyl-4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-imidazole

7-Bromo-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine (1.5 g, 4 mmole) in DMF (30 ml) was treated with excess gaseous methylamine at room temperature and stirred overnight. The excess methylamine was removed at 40°C in vacuo and the solution cooled to 0°C. Thionyl chloride (0.75 ml) was added and the solution stirred at room temperature for 30 minutes. Water (60 ml) was added, the mixture stirred at 0-5°C for 2 hours and then filtered. The solid was washed with water (10 ml) and dried in vacuo at 50°C, to give the product (1.21 g, 72%) as a solid, m.p. 177-180°C.

EXAMPLE 29

1-(2-Methylcarboxamidophenyl)-5-chloromethyl-4-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-imidazole

3-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-5,6-dihydro-6-oxo-4H-imidazo[1,5-a][4,1]benzoxazepine (1.08 g, 3.5 mmole) in DMF (45 ml) was treated with excess gaseous methylamine at room temperature and stirred overnight. The excess methylamine was removed at 40°C in vacuo and the solution cooled to 0°C. Thionyl chloride (0.5 ml) was added and the solution stirred at room temperature for 30 minutes. Water (65 ml) was added, the mixture stirred at 0-5°C for 2 hours and then filtered. The solid was washed with water (10 ml) and dried in vacuo at 50°C, to give the product (0.87 g, 69%) as a solid, m.p. 188-189°C.

EXAMPLE 30

7-Bromo-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine (I)

1-(3-Bromo-2-methylcarboxamidophenyl)-5-chloromethyl-4-(5-cyclopropyl-1,2,4-oxadiazole-3-yl)imidazole (0.88 g, 2 mmole) in THF (25 ml) at -30°C was treated with potassium t-butoxide (0.3 g, 2.6 mmole) in THF (25 ml) added over 1 hour. Acetic acid (0.5 ml) was added, and the solvent removed in vacuo. Water (25 ml) was added to the residual oil which solidified when cooled in ice. The resulting mixture was aged in ice for 2 hours, filtered, washed with water (10 ml) and dried in vacuo at 50°C overnight to give the crude product (0.813 g, 100%). The solid was chromatographed on silica with ethyl acetate to give product (0.74 g, 92%) as a yellow solid which was recrystallised from isopropanol/methanol (3/2) to give the pure product (0.52 g) as an off-white solid, m.p. 213-215°C. $M^{+\cdot}$ = 399:401 (1:1).

EXAMPLE 31

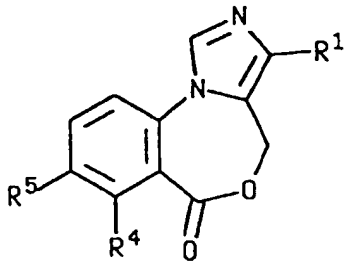
3-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine (I)

1-(2-Methylcarboxamidophenyl)-5-chloromethyl-4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)imidazole (0.64 g, 1.8 mmole) in THF (25 ml) at -30°C was treated with potassium t-butoxide (0.3 g, 2.6 mmole) in THF (25 ml) added over 1 hour. Acetic acid (0.5 ml) was added, and the solvent removed in vacuo. Water (25 ml) was added to the residual oil which solidified when cooled in ice. The resulting mixture was aged in ice for 2 hours, filtered, washed with water (10 ml) and dried in vacuo at 50°C overnight to give the crude product (0.5 g, 86%) which was recrystallised from isopropanol/methanol (3/2) to give the pure product (0.3 g) as an off-white solid, m.p. 189-190°C. $M^{+\cdot}$ = 321.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound of formula III:



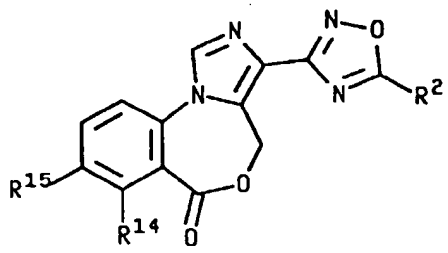
(III)

wherein R^1 is an aromatic heterocyclic group containing 5 or 6 atoms, up to 3 of which are selected from oxygen, nitrogen and sulphur, any of which groups may be unsubstituted or substituted on a carbon atom by a substituent selected from C_{1-5}alkyl, C_{3-6}cycloalkyl, trifluoromethyl, phenyl, amino, C_{1-6}alkylamino, C_{1-6}alkoxyC_{1-6}alkyl or hydroxy; and R^4 and R^5 each independently signify hydrogen, halogen, trifluoromethyl, cyano, nitro, amino or C_{1-6}alkyl.

2. A compound as claimed in claim 1 wherein R^4 and R^5 independently represent hydrogen, halogen or trifluoromethyl.

3. A compound as claimed in claim 1 or claim 2 wherein R^1 represents 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-3-yl, 1,3,4-thiadiazol-2-yl or 1,2,5-thiadiazol-3-yl, any of which groups may be optionally substituted as defined in claim 1.

4. A compound as claimed in claim 1 represented by formula IV:

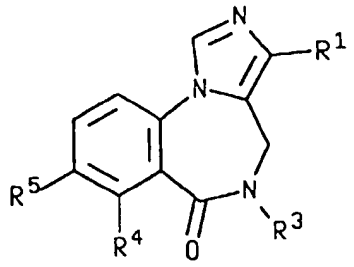


(IV)

wherein R^{14} and R^{15} independently represent hydrogen, fluoro, chloro or bromo; and R^2 represents hydrogen, C_{1-4} alkyl or C_{3-6} cycloalkyl.

5. A compound as claimed in claim 4 wherein R^2 represents hydrogen, methyl, n-propyl, isopropyl, t-butyl or cyclopropyl.

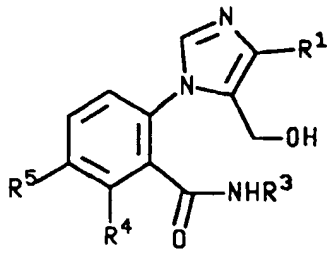
6. A process for the preparation of a compound of formula I:



(I)

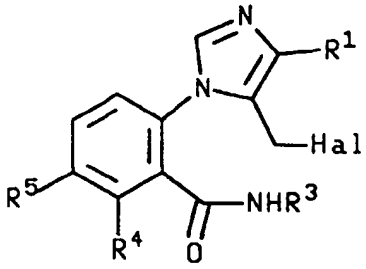
wherein R^1, R^4 and R^5 are as defined in claim 1; and R^3 represents hydrogen or C_{1-6}alkyl; which process comprises the following steps:

a) aminolysis of a benzoxazepinone of formula III as defined in claim 1 to form an amide of formula V:



(V)

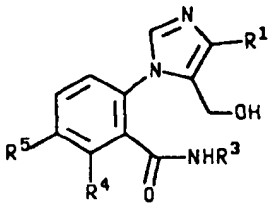
wherein R^1, R^4 and R^5 are as defined in claim 1; and R^3 represents hydrogen or C_{1-6} alkyl;
b) halogenation of compound V to form a compound of formula VI:



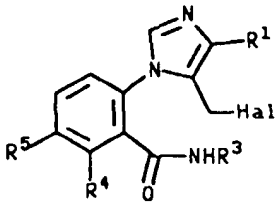
(VI)

wherein R^1, R^3, R^4 and R^5 are as defined above; and Hal represents chlorine or bromine; and
c) cyclisation of compound VI to form a compound of formula I.

7. A compound of formula V or of formula VI:



(V)

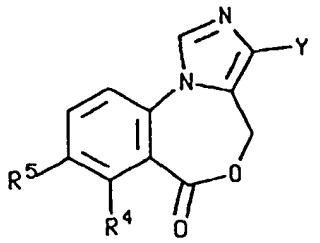


(VI)

wherein R^1, R^4 and R^5 are as defined in claim 1; and R^3 represents hydrogen or C_{1-6}alkyl.

8. A process for the preparation of a compound as claimed in any one of claims 1 to 5, which process comprises:

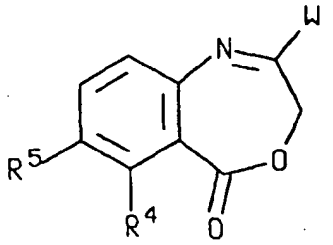
(a) converting a compound of formula VII:



(VII)

wherein R^4 and R^5 are as defined in claim 1, and Y represents a group selected from -CN, $-CONH_2$, $-C(NH_2)=NOH$ and $-COR^a$, where R^a represents a leaving group; into a corresponding compound in which Y represents an aromatic heterocylic ring containing 5 or 6 atoms as defined in claim 1; or

(b) reacting an isocyanide of formula $CN-CH_2-R^1$ with a compound of formula VIII:

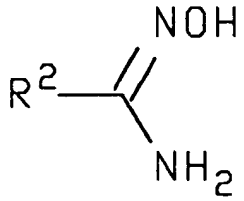


(VIII)

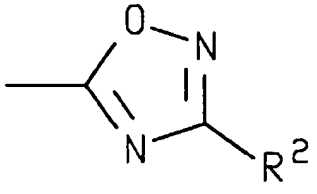
wherein R^1, R^4 and R^5 are as defined in claim 1, and W represents a leaving group; in the presence of a base.

9. A process as claimed in claim 8 for the preparation of a compound as claimed in claim 1 wherein R^1 represents oxadiazolyl, which process comprises:

(i) reacting a reactive derivative of a compound of formula VII as defined in claim 8 wherein Y represents $-CO_2H$, with a compound of formula:

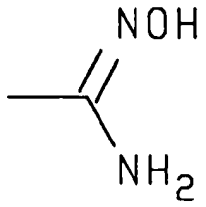


wherein R^2 is as defined in claim 4; to form a compound of formula III wherein R^1 is:

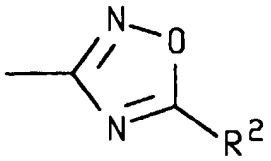


in which R^2 is as defined in claim 4; or

(ii) reacting a compound of formula VII as defined in claim 8 wherein Y represents -CN, with hydroxylamine or a salt thereof; to form a compound of formula VII wherein Y represents:



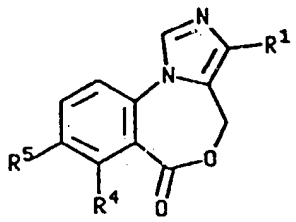
and reacting that product with an anhydride of formula $(R^2CO)_2O$, wherein R^2 is as defined in claim 4; to form a compound of formula III wherein R^1 is:



in which R^2 is as defined in claim 4.

Claims for the following Contracting State : ES

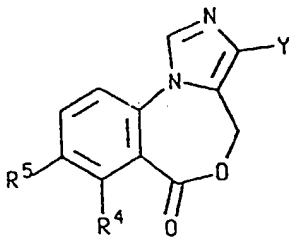
1. A process for the preparation of a compound of formula III:



(III)

wherein R^1 is an aromatic heterocyclic group containing 5 or 6 atoms, up to 3 of which are selected from oxygen, nitrogen and sulphur, any of which groups may be unsubstituted or substituted on a carbon atom by a substituent selected from C_{1-5}alkyl, C_{3-6}cycloalkyl, trifluoromethyl, phenyl, amino, C_{1-6}alkylamino, C_{1-6}alkoxyC_{1-6}alkyl or hydroxy; and R^4 and R^5 each independently signify hydrogen, halogen, trifluoromethyl, cyano, nitro, amino or C_{1-6}alkyl; which process comprises

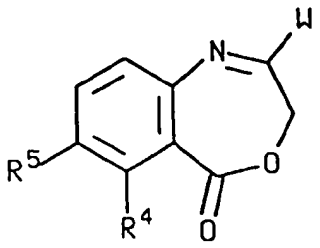
(a) converting a compound of formula VII:



(VII)

wherein R^4 and R^5 are as defined above, and Y represents a group selected from -CN, $-CONH_2$, $-C(NH_2)$ =NOH and $-COR^a$, where R^a represents a leaving group; into a corresponding compound in which Y represents an aromatic heterocylic ring containing 5 or 6 atoms as defined above; or

(b) reacting an isocyanide of formula $CN\text{-}CH_2\text{-}R^1$ with a compound of formula VIII:



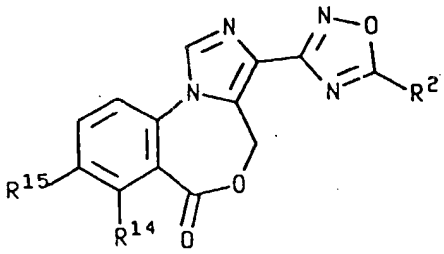
(VIII)

wherein R^1, R^4 and R^5 are as defined above, and W represents a leaving group; in the presence of a base.

2. A process as claimed in claim 1 for the preparation of a compound wherein R^4 and R^5 independently represent hydrogen, halogen or trifluoromethyl.

3. A process as claimed in claim 1 or claim 2 for the preparation of a compound wherein R^1 represents 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-3-yl, 1,3,4-thiadiazol-2-yl or 1,2,5-thiadiazol-3-yl, any of which groups may be optionally substituted as defined in claim 1.

4. A process as claimed in claim 1 for the preparation of a compound represented by formula IV:



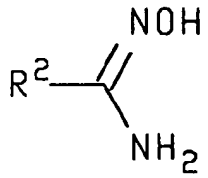
(IV)

wherein R^{14} and R^{15} independently represent hydrogen, fluoro, chloro or bromo; and R^2 represents hydrogen, C_{1-4} alkyl or C_{3-6} cycloalkyl.

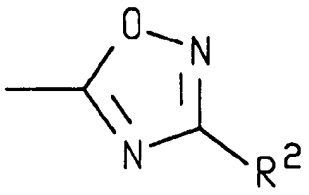
5. A process as claimed in claim 4 for the preparation of a compound wherein R^2 represents hydrogen, methyl, n-propyl, isopropyl, t-butyl or cyclopropyl.

6. A process as claimed in claim 1 for the preparation of a compound of formula III wherein R^1 represents oxadiazolyl, which process comprises:

(i) reacting a reactive derivative of a compound of formula VII as defined in claim 1 wherein Y represents $-CO_2H$, with a compound of formula:

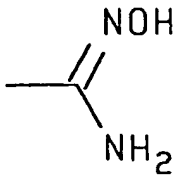


wherein R^2 is as defined in claim 4; to form a compound of formula III wherein R^1 is:

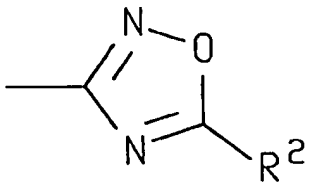


in which R^2 is as defined in claim 4; or

(ii) reacting a compound of formula VII as defined in claim 1 wherein Y represents -CN, with hydroxylamine or a salt thereof; to form a compound of formula VII wherein Y represents:

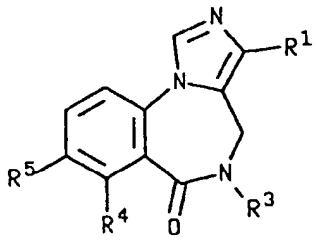


and reacting that product with an anhydride of formula $(R^2CO)_2O$, wherein R^2 is as defined in claim 4; to form a compound of formula III wherein R^1 is:



in which R^2 is as defined in claim 4.

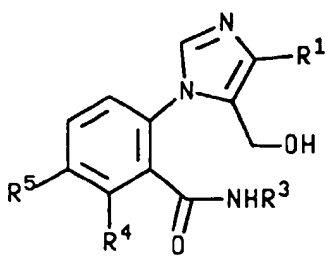
7. A process for the preparation of a compound of formula I:



(I)

wherein R^1, R^4 and R^5 are as defined in claim 1; and R^3 represents hydrogen or C_{1-6}alkyl; which process comprises the following steps:

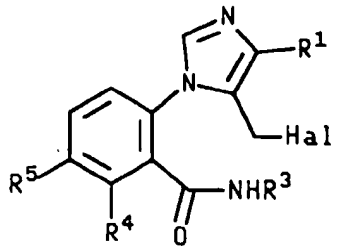
a) aminolysis of a benzoxazepinone of formula III as defined in claim 1 to form an amide of formula V:



(V)

wherein R^1, R^4 and R^5 are as defined in claim 1; and R^3 represents hydrogen or C_{1-6} alkyl;

b) halogenation of compound V to form a compound of formula VI:



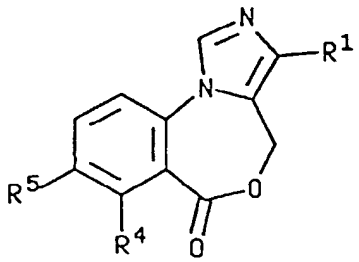
(VI)

wherein R^1, R^3, R^4 and R^5 are as defined above; and Hal represents chlorine or bromine; and
c) cyclisation of compound VI to form a compound of formula I.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Eine Verbindung der Formel III:



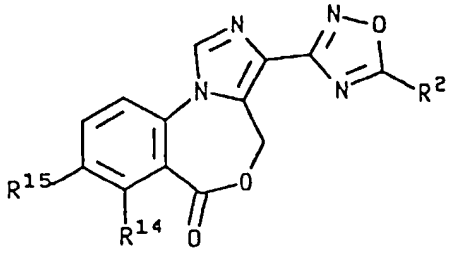
(III)

worin R^1 eine aromatische heterocyclische Gruppe ist, die 5 oder 6 Atome enthält, wobei bis zu 3 davon ausgewählt sind aus Sauerstoff, Stickstoff und Schwefel, wobei jede dieser Gruppen unsubstituiert oder an einem Kohlenstoffatom durch einen Substituenten, ausgewählt aus C_{1-5}-Alkyl, C_{3-6}-cycloalkyl, Trifluormethyl, Phenyl, Amino, C_{1-6}-Alkylamino, C_{1-6}-Alkoxy-C_{1-6}-alkyl oder Hydroxy, substituiert sein kann, und R^4 und R^5 jedes unabhängig voneinander Wasserstoff, Halogen, Trifluormethyl, Cyano, Nitro, Amino oder C_{1-6}-Alkyl bedeutet.

2. Eine Verbindung wie in Anspruch 1 beansprucht, worin R^4 und R^5 unabhängig voneinander Wasserstoff, Halogen oder Trifluormethyl bedeuten.

3. Eine Verbindung wie in Anspruch 1 oder Anspruch 2 beansprucht, worin R^1 1,2,4-Oxadiazol-3-yl, 1,2,4-Oxadiazol-5-yl, 1,3,4-Oxadiazol-2-yl, 1,2,4-Thiadiazol-3-yl, 1,3,4-Thiadiazol-2-yl oder 1,2,5-Thiadiazol-3-yl bedeutet, wobei jede dieser Gruppen gegebenenfalls wie in Anspruch 1 definiert substituiert sein kann.

4. Eine Verbindung wie in Anspruch 1 beansprucht, die durch Formel IV dargestellt ist:

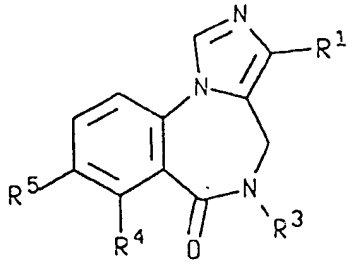


(IV)

worin R^{14} und R^{15} unabhängig voneinander Wasserstoff, Fluor, Chlor oder Brom bedeuten, und R^2 Wasserstoff, C_{1-4}-Alkyl oder C_{3-6}-Cycloalkyl bedeutet.

5. Eine Verbindung wie in Anspruch 4 beansprucht, worin R^2 Wasserstoff, Methyl, n-Propyl, Isopropyl, t-Butyl oder Cyclopropyl bedeutet.

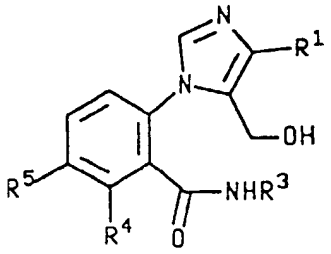
6. Ein Verfahren zur Herstellung einer Verbindung der Formel I:



(I)

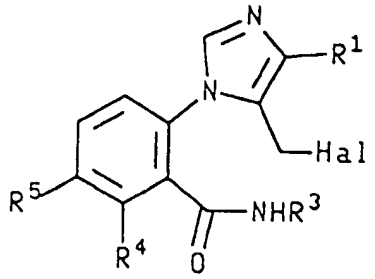
worin R^1, R^4 und R^5 wie in Anspruch 1 definiert sind, und R^3 Wasserstoff oder C_{1-6}-Alkyl bedeutet, wobei das Verfahren die folgenden Schritte umfaßt:

a) Aminolyse eines Benzoxazepinons der Formel III, das wie in Anspruch 1 definiert ist, um ein Amid der Formel V zu bilden:



(V)

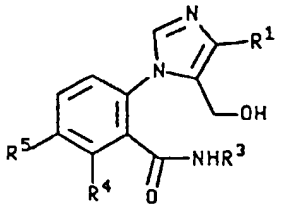
worin R^1, R^4 und R^5 wie in Anspruch 1 definiert sind, und R^3 Wasserstoff oder C_{1-6}-Alkyl bedeutet,
b) Halogenierung der Verbindung V, um eine Verbindung der Formel VI zu bilden:



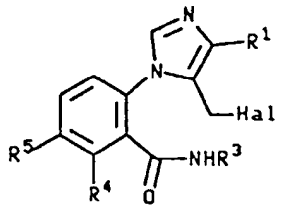
(VI)

worin R^1, R^3, R^4 und R^5 wie oben definiert sind, und Hal Chlor oder Brom bedeutet, und
c) Cyclisierung der Verbindung VI, um eine Verbindung der Formel I zu bilden.

7. Eine Verbindung der Formel V oder der Formel VI:



(V)

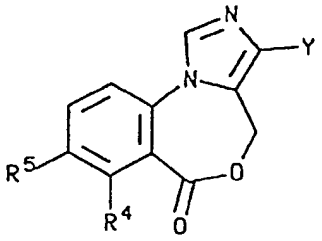


(VI)

worin R^1, R^4 und R^5 wie in Anspruch 1 definiert sind, und R^3 Wasserstoff oder C_{1-6}-Alkyl bedeutet.

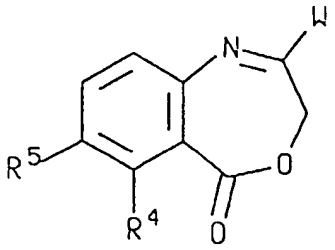
8. Ein Verfahren zur Herstellung einer Verbindung wie in irgendeinem der Ansprüche 1 bis 5 beansprucht, wobei das Verfahren umfaßt:

(a) die Umwandlung einer Verbindung der Formel VII:



(VII)

worin R^4 und R^5 wie in Anspruch 1 definiert sind, und Y eine Gruppe, ausgewählt aus -CN, $-CONH_2$, $-C(NH_2)=NOH$ und $-COR^a$, wobei R^a eine Abgangsgruppe darstellt, bedeutet, in eine entsprechende Verbindung, in der Y einen wie in Anspruch 1 definierten aromatischen heterocyclischen Ring darstellt, der 5 oder 6 Atome enthält, oder
(b) die Umsetzung eines Isocyanids der Formel $CN-CH_2-R^1$ mit einer Verbindung der Formel VIII:

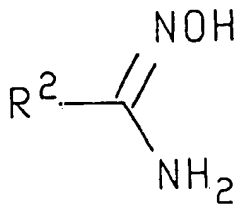


(VIII)

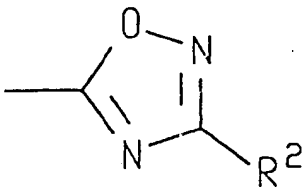
worin R^1, R^4 und R^5 wie in Anspruch 1 definiert sind, und W eine Abgangsgruppe darstellt, in Gegenwart einer Base.

9. Ein Verfahren wie in Anspruch 8 beansprucht zur Herstellung einer Verbindung nach Anspruch 1, worin R^1 Oxadiazolyl bedeutet, wobei das Verfahren umfaßt:

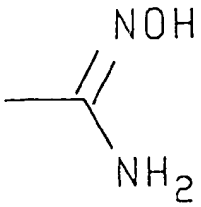
(i) die Umsetzung eines reaktiven Derivats einer Verbindung der Formel VII, die wie in Anspruch 8 definiert ist, worin Y $-CO_2H$ bedeutet, mit einer Verbindung der Formel:



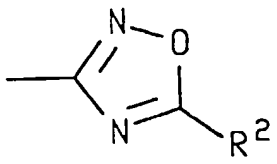
worin R^2 wie in Anspruch 4 definiert ist, um eine Verbindung der Formel III zu bilden, worin R^1



ist, worin R^2 wie in Anspruch 4 definiert ist, oder
(ii) die Umsetzung einer Verbindung der Formel VII, die wie in Anspruch 8 definiert ist, worin Y -CN bedeutet, mit Hydroxylamin oder einem Salz davon, um eine Verbindung der Formel VII zu bilden, worin Y



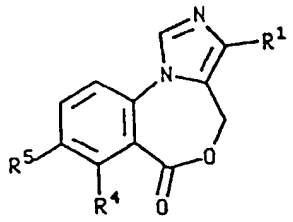
bedeutet, und die Umsetzung dieses Produkts mit einem Anhydrid der Formel $(R^2CO)_2O$, worin R^2 wie in Anspruch 4 definiert ist, um eine Verbindung der Formel III zu bilden, worin R^1



ist, worin R^2 wie in Anspruch 4 definiert ist.

Patentansprüche für folgenden Vertragsstaat : ES

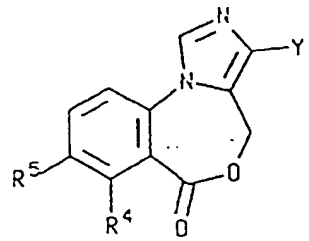
1. Ein Verfahren zur Herstellung einer Verbindung der Formel III:



(III)

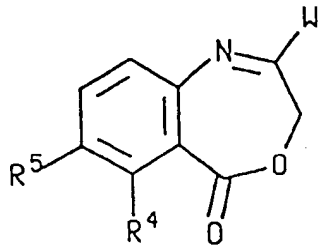
worin R^1 eine aromatische heterocyclische Gruppe ist, die 5 oder 6 Atome enthält, wobei bis zu 3 davon ausgewählt sind aus Sauerstoff, Stickstoff und Schwefel, wobei jede dieser Gruppen unsubstituiert oder an einem Kohlenstoffatom durch einen Substituenten, ausgewählt aus C_{1-5}-Alkyl, C_{3-6}-Cycloalkyl, Trifluormethyl, Phenyl, Amino, C_{1-6}-Alkylamino, C_{1-6}-Alkoxy-C_{1-6}-alkyl oder Hydroxy, substituiert sein kann, und R^4 und R^5 jedes unabhängig voneinander Wasserstoff, Halogen, Trifluormethyl, Cyano, Nitro, Amino oder C_{1-6}-Alkyl bedeutet, wobei dieses Verfahren umfaßt:

(a) die Umwandlung einer Verbindung der Formel VII:



(VII)

worin R^4 und R^5 wie oben definiert sind, und Y eine Gruppe, ausgewählt aus -CN, $-CONH_2$, $-C(NH_2)=NOH$ und $-COR^a$, wobei R^a eine Abgangsgruppe darstellt, bedeutet, in eine entsprechende Verbindung, in der Y einen wie oben definierten aromatischen heterocyclischen Ring darstellt, der 5 oder 6 Atome enthält, oder
(b) die Umsetzung eines Isocyanids der Formel $CN-CH_2-R^1$ mit einer Verbindung der Formel VIII:



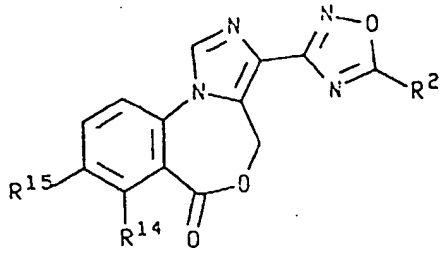
(VIII)

worin R^1, R^4 und R^5 wie oben definiert sind, und W eine Abgangsgruppe darstellt, in Gegenwart einer Base.

2. Ein Verfahren wie in Anspruch 1 beansprucht zur Herstellung einer Verbindung, worin R^4 und R^5 unabhängig voneinander Wasserstoff, Halogen oder Trifluormethyl bedeuten.

3. Ein Verfahren wie in Anspruch 1 oder Anspruch 2 beansprucht zur Herstellung einer Verbindung, worin R^1 1,2,4-Oxadiazol-3-yl, 1,2,4-Oxadiazol-5-yl, 1,3,4-Oxadiazol-2-yl, 1,2,4-Thiadiazol-3-yl, 1,3,4-Thiadiazol-2-yl oder 1,2,5-Thiadiazol-3-yl bedeutet, wobei jede dieser Gruppen gegebenenfalls wie in Anspruch 1 definiert substituiert sein kann.

4. Ein Verfahren wie in Anspruch 1 beansprucht zur Herstellung einer Verbindung, die durch Formel IV dargestellt ist:



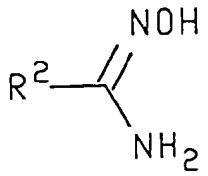
(IV)

worin R^{14} und R^{15} unabhängig voneinander Wasserstoff, Fluor, Chlor oder Brom bedeuten, und R^2 Wasserstoff, C_{1-4}-Alkyl oder C_{3-6}-Cycloalkyl bedeutet.

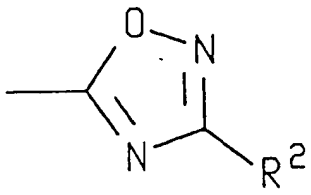
5. Ein Verfahren wie in Anspruch 4 beansprucht zur Herstellung einer Verbindung, worin R^2 Wasserstoff, Methyl, n-Propyl, Isopropyl, t-Butyl oder Cyclopropyl bedeutet.

6. Ein Verfahren wie in Anspruch 1 beansprucht zur Herstellung einer Verbindung der Formel III, worin R^1 Oxadiazolyl bedeutet, wobei das Verfahren umfaßt:

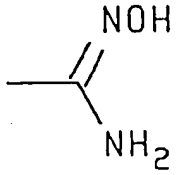
(i) die Umsetzung eines reaktiven Derivats einer Verbindung der Formel VII, die wie in Anspruch 1 definiert ist, worin Y $-CO_2H$ bedeutet, mit einer Verbindung der Formel:



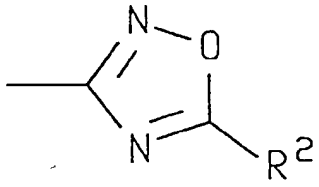
worin R^2 wie in Anspruch 4 definiert ist, um eine Verbindung der Formel III zu bilden, worin R^1



ist, worin R^2 wie in Anspruch 4 definiert ist, oder
(ii) die Umsetzung einer Verbindung der Formel VII, die wie in Anspruch 1 definiert ist, worin Y -CN bedeutet, mit Hydroxylamin oder einem Salz davon, um eine Verbindung der Formel VII zu bilden, worin Y

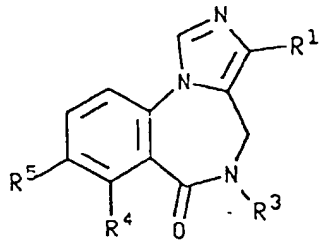


bedeutet, und die Umsetzung dieses Produkts mit einem Anhydrid der Formel $(R^2CO)_2O$, worin R^2 wie in Anspruch 4 definiert ist, um eine Verbindung der Formel III zu bilden, worin R^1



ist, worin R^2 wie in Anspruch 4 definiert ist.

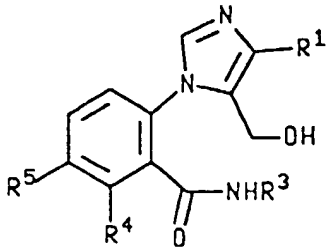
7. Ein Verfahren zur Herstellung einer Verbindung der Formel I:



(I)

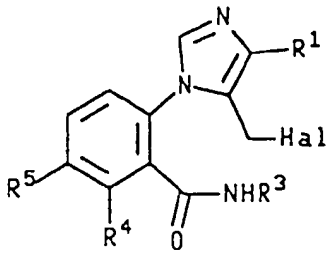
worin R^1, R^4 und R^5 wie in Anspruch 1 definiert sind, und R^3 Wasserstoff oder C_{1-6}-Alkyl bedeutet, wobei das Verfahren die folgenden Schritte umfaßt:

a) Aminolyse eines Benzoxazepinons der Formel III, das wie in Anspruch 1 definiert ist, um ein Amid der Formel V zu bilden:



(V)

worin R^1, R^4 und R^5 wie in Anspruch 1 definiert sind, und R^3 Wasserstoff oder C_{1-6}-Alkyl bedeutet,
b) Halogenierung der Verbindung V, um eine Verbindung der Formel VI zu bilden:



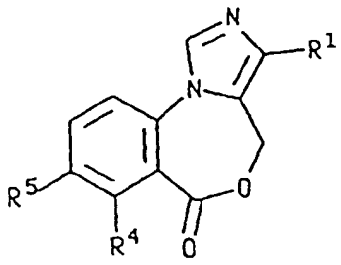
(VI)

worin R^1, R^3, R^4 und R^5 wie oben definiert sind, und Hal Chlor oder Brom bedeutet, und
c) Cyclisierung der Verbindung VI, um eine Verbindung der Formel I zu bilden.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Un composé de la formule III:



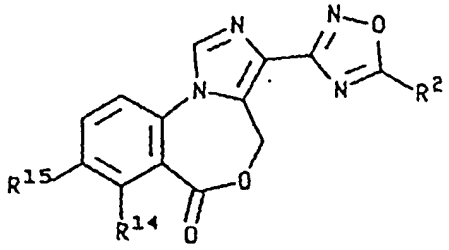
(III)

dans laquelle R^1 est un groupe hétérocyclique renfermant 5 ou 6 atomes, dont 3 au maximum sont choisis parmi l'oxygène, l'azote et le soufre, l'un quelconque de ces groupes pouvant être non substitué ou substitué sur un atome de carbone par un substituant choisi parmi les groupes alkyle en C_1 à C_5, cycloalkyle en C_3 à C_6, trifluorométhyle, phényle, amino, alkylamino en C_1 à C_6, alcoxy (en C_1 à C_6)-alkyle en C_1 à C_6 ou hydroxy; et R^4 et R^5 signifient, chacun de façon indépendante, l'hydrogène, un groupe halogène, trifluorométhyle, cyano, nitro, amino ou alkyle en C_1 à C_6.

2. Un composé tel que revendiqué dans la revendication 1, dans lequel R^4 et R^5 représentent indépendamment de l'hydrogène, de l'halogène ou du trifluorométhyle.

3. Un composé tel que revendiqué dans la revendication 1 ou la revendication 2, dans lequel R^1 représente un groupe 1,2,4-oxadiazol-3-yle, 1,2,4-oxadiazol-5-yle, 1,3,4-oxadiazol-2-yle, 1,2,4-thiadiazol-3-yle, 1,3,4-thiadiazol-2-yle ou 1,2,5-thiadiazol-3-yle, l'un quelconque de ces groupes pouvant être substitués facultativement comme spécifié dans la revendication 1.

4. Un composé tel que revendiqué dans la revendication 1, représenté par la formule IV:

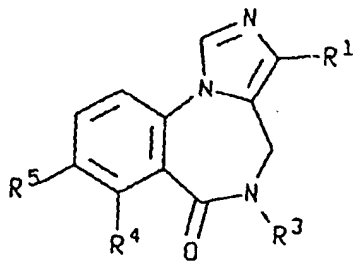


(IV)

dans laquelle R^{14} et R^{15} représentent indépendamment de l'hydrogène, du fluor, du chlore ou du brome; et R^2 représente de l'hydrogène, un groupe alkyle en C_1 à C_4 ou cycloalkyle en C_3 à C_6.

5. Un composé tel que revendiqué dans la revendication 4, dans lequel R^2 représente de l'hydrogène, du méthyle, du n-propyle, de l'isopropyle, du t-butyle ou du cyclopropyle.

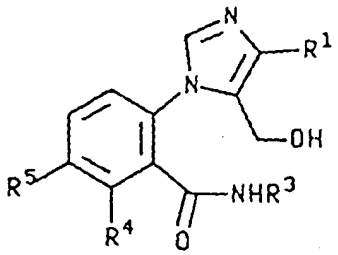
6. Un procédé pour la préparation d'un composé de formule I:



(I)

dans laquelle R^1, R^4 et R^5 sont tels que définis dans la revendication 1; et R^3 représente de l'hydrogène ou un alkyle en C_1 à C_6, lequel procédé comportant des étapes suivantes:

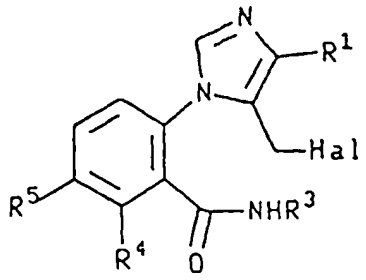
a) l'aminolyse d'une benzoxazépinone de formule III tel que défini dans la revendication 1 pour former un amide de formule V:



(V)

dans laquelle R^1, R^4 et R^5 sont tels que définis dans la revendication 1; et R^3 représente de l'hydrogène ou un alkyle en C_1 à C_6;

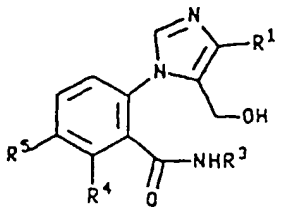
b) l'halogénation du composé V pour former un composé de la formule VI:



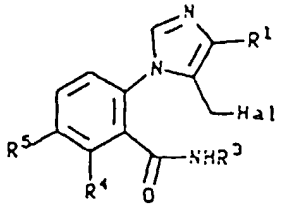
(VI)

dans laquelle R^1, R^3, R^4 et R^5 sont tels que définis ci-dessus, et Hal représente du chlore ou du brome; et
c) la cyclisation du composé VI pour former un composé de la formule I.

7. Un composé de formule V ou de la formule VI:



(V)

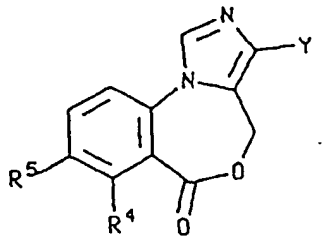


(VI)

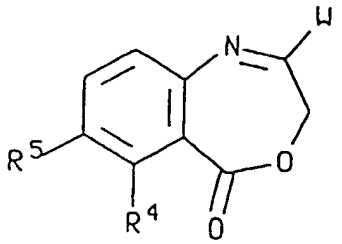
dans lesquelles R^1, R^4 et R^5 sont tels que définis dans la revendication 1, et R^3 représente de l'hydrogène ou un alkyle en C_1 à C_6.

8. Un procédé pour la préparation d'un composé tel que revendiqué dans l'une quelconque des revendications 1 à 5, procédé selon lequel:

(a) on convertit un composé de formule VII:



dans laquelle R^4 et R^5 sont tels que définis dans la revendication 1, et Y représente un groupe choisi parmi -CN, $-CONH_2$, $-C(NH_2)=NOH$ et $-COR^a$, où R^a représente un groupe partant, en un composé correspondant dans lequel Y représente un noyau aromatique hétérocyclique renfermant 5 ou 6 atomes tels que décrits dans la revendication 1; ou
(b) on fait réagir un isocyanide de formule $CN-CH_2-R^1$ avec un composé de formule VIII:

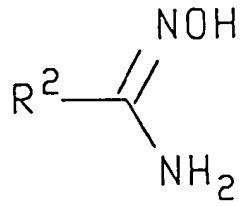


(VIII)

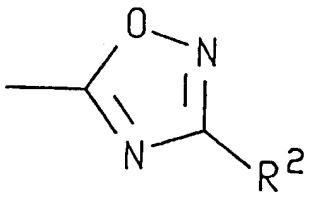
dans laquelle R^1, R^4 et R^5 sont tels que définis dans la revendication 1, et W représente un groupe partant, en présence d'une base.

9. Un procédé tel que revendiqué dans la revendication 8 pour la préparation d'un composé tel que revendiqué dans la revendication 1, dans lequel R^1 représente un groupe oxadiazolyle, procédé selon lequel:

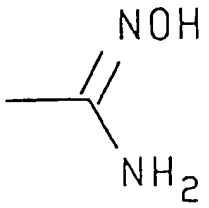
(i) on fait réagir un dérivé réactif d'un composé de formule VII tel que défini dans la revendication 8, dans laquelle Y représente $-CO_2H$ avec un composé de formule:



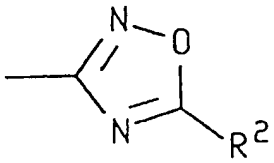
dans laquelle R^2 est tel que défini dans la revendication 4, pour former un composé de formule III dans laquelle R^1 est:



dans laquelle R^2 est tel que défini dans la revendication 4; ou
(ii) on fait réagir un composé de formule VII tel que défini dans la revendication 8 dans laquelle Y représente -CN, avec une hydroxylamine ou un de ses sels de ceux-ci, afin de former un composé de la formule VII dans laquelle Y représente:



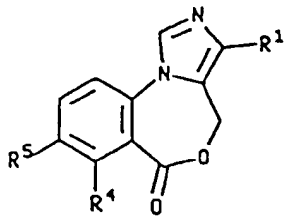
après quoi on fait réagir ce produit avec un anhydride de formule $(R^2CO)_2O$, dans laquelle R^2 est tel que défini dans la revendication 4, afin de former un composé de formule III dans laquelle R^1 est:



formule dans laquelle R^2 est tel que défini dans la revendication 4.

Revendications pour l'Etat contractant suivant : ES

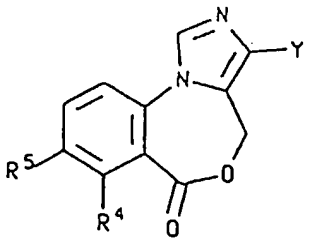
1. Un procédé pour la préparation d'un composé de la formule III:



(III)

dans laquelle R^1 est un groupe hétérocyclique renfermant 5 ou 6 atomes, dont 3 au maximum sont choisis parmi l'oxygène, l'azote et le soufre, l'un quelconque de ces groupes pouvant être non substitué ou substitué sur un atome de carbone par un substituant choisi parmi les groupes alkyle en C_1 à C_5, cycloalkyle en C_3 à C_6, trifluorométhyle, phényle, amino, alkylamino en C_1 à C_6, alcoxy (en C_1 à C_6)-alkyle en C_1 à C_6 ou hydroxy; et R^4 et R^5 signifient, chacun de façon indépendante, l'hydrogène, un groupe halogène, trifluorométhyle, cyano, nitro, amino ou alkyle en C_1 à C_6, procédé selon lequel:

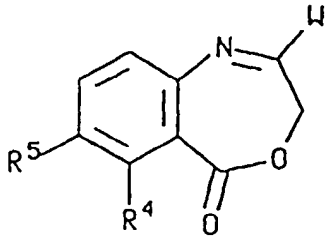
(a) on convertit un composé de formule VII:



(VII)

dans laquelle R^4 et R^5 sont tels que définis dans la revendication 1, et Y représente un groupe choisi parmi -CN, $-CONH_2$, $-C(NH_2)=NOH$ et $-COR^a$, où R^a représente un groupe partant, en un composé correspondant dans lequel Y représente un noyau aromatique hétérocyclique renfermant 5 ou 6 atomes tels que décrits dans la revendication 1; ou

(b) on fait réagir un isocyanide de formule $CN-CH_2-R^1$ avec un composé de formule VIII:



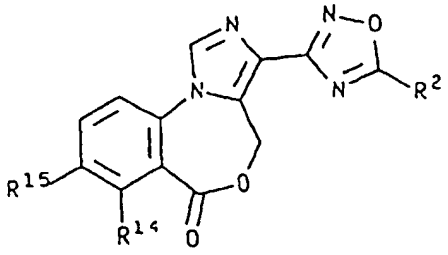
(VIII)

dans laquelle R^1, R^4 et R^5 sont tels que définis ci-dessus, et W représente un groupe partant, en présence d'une base.

2. Un procédé tel que revendiqué dans la revendication 1 pour la préparation d'un composé dans lequel R^4 et R^5 représentent indépendamment de l'hydrogène, de l'halogène ou du trifluorométhyle.

3. Un procédé tel que revendiqué dans la revendication 1 ou la revendication 2 pour la préparation d'un composé dans lequel R^1 représente un groupe 1,2,4-oxadiazol-3-yle, 1,2,4-oxadiazol-5-yle, 1,3,4-oxadiazol-2-yle, 1,2,4-thiadiazol-3-yle, 1,3,4-thiadiazol-2-yle ou 1,2,5-thiadiazol-3-yle, l'un quelconque de ces groupes pouvant être substitués facultativement comme spécifié dans la revendication 1.

4. Un procédé tel que revendiqué dans la revendication 1 pour la préparation d'un composé représenté par la formule IV:



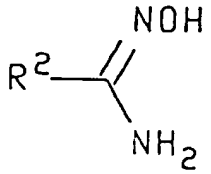
(IV)

dans laquelle R^{14} et R^{15} représentent indépendamment de l'hydrogène, du fluor, du chlore ou du brome; et R^2 représente de l'hydrogène, un groupe alkyle en C_1 à C_4 ou cycloalkyle en C_3 à C_6.

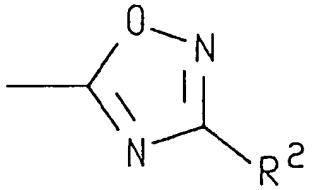
5. Un procédé tel que revendiqué dans la revendication 4 pour la préparation d'un composé dans lequel R^2 représente de l'hydrogène, du méthyle, du n-propyle, de l'isopropyle, du t-butyle ou du cyclopropyle.

6. Un procédé tel que revendiqué dans la revendication 1 pour la préparation d'un composé de formule III, dans laquelle R^1 représente un groupe oxadiazolyle, procédé selon lequel:

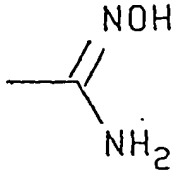
(i) on fait réagir un dérivé réactif d'un composé de formule VII tel que défini dans la revendication 1, dans laquelle Y représente $-CO_2H$ avec un composé de formule:



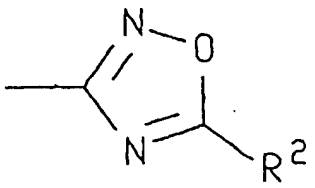
dans laquelle R^2 est tel que défini dans la revendication 4, pour former un composé de formule III dans laquelle R^1 est:



formule dans laquelle R^2 est tel que défini dans la revendication 4; ou
(ii) on fait réagir un composé de formule VII tel que défini dans la revendication 8 dans laquelle Y représente -CN, avec une hydroxylamine ou un de ses sels, afin de former un composé de la formule VII dans laquelle Y représente:

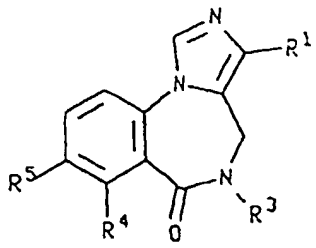


après quoi on fait réagir ce produit avec un anhydride de formule $(R^2CO)_2O$, dans laquelle R^2 est tel que défini dans la revendication 4, afin de former un composé de formule III dans laquelle R^1 est:



dans laquelle R^2 est tel que défini dans la revendication 4.

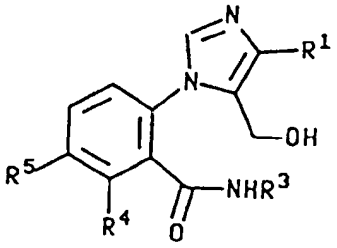
7. Un procédé pour la préparation d'un composé de formule I:



(I)

dans laquelle R^1, R^4 et R^5 sont tels que définis dans la revendication 1; et R^3 représente de l'hydrogène ou un alkyle en C_1 à C_6, lequel procédé comportant des étapes suivantes:

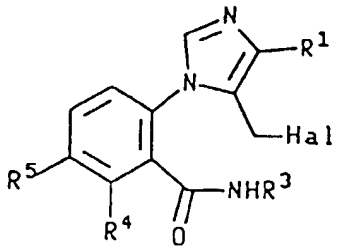
a) l'aminolyse d'une benzoxazépinone de formule III tel que défini dans la revendication 1 pour former un amide de formule V:



(V)

dans laquelle R^1, R^4 et R^5 sont tels que définis dans la revendication 1; et R^3 représente de l'hydrogène ou un alkyle en C_1 à C_6;

b) l'halogénation du composé V pour former un composé de la formule VI:



(VI)

dans laquelle R^1, R^3, R^4 et R^5 sont tels que définis ci-dessus, et Hal représente du chlore ou du brome; et

c) la cyclisation du composé VI pour former un composé de la formule I.